Stenotrophomonas maltophilia

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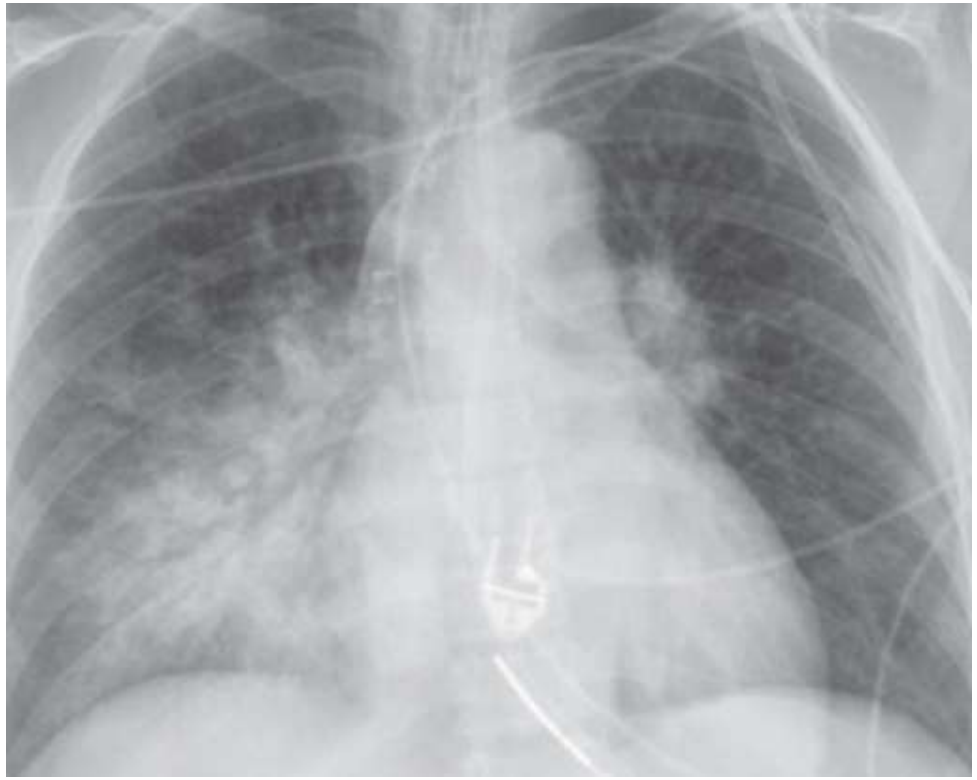
Caso clinico (1)

- Uomo di 77 anni, affetto da BPCO e da diabete mellito
- Ricovero in Rianimazione per incidente automobilistico e sottoposto a IOT
- Dopo 7 giorni: febbre 38.1°, ↑PCR 38.5 mg/dl (v.n. 0.5), ↑GB 18000/µl
- Aumento secrezioni respiratorie
- Rx torace:
  - infiltrato polmonare base dx;



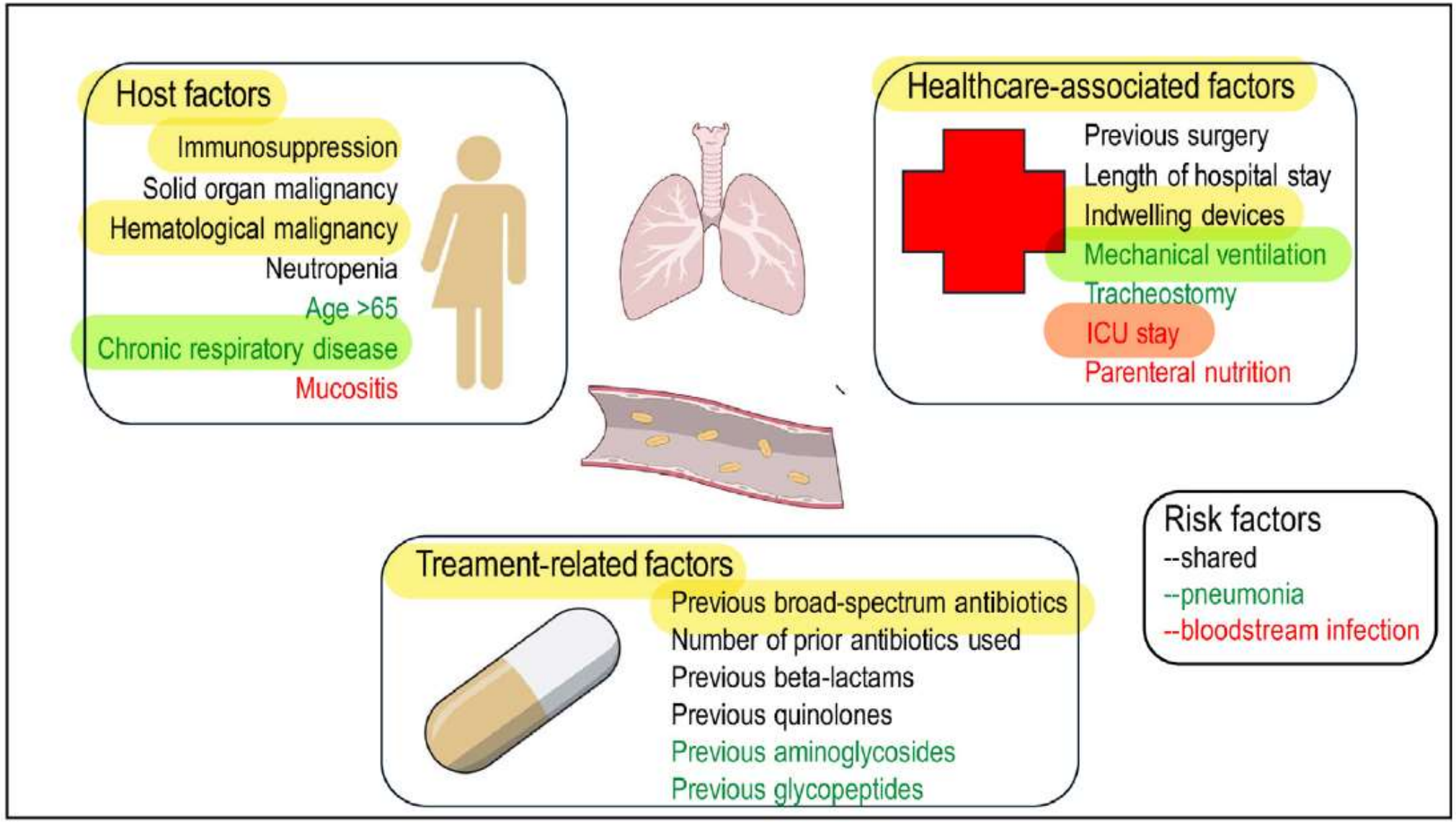
Caso clinico (2)

- BAL: Filmarray positivo per *Pseudomonas aeruginosa*
- Terapia: piperacillina-tazobactam 4.5 g/6h
- Colturale BAL : a circa 48 ore positivo per *Pseudomonas aeruginosa* e *Stenotrophomonas maltophilia,* ABG *in corso*; PAZIENTE STABILE
- *Stenotrophomonas maltophilia* considerata colonizzante
- Emocolture: *in corso*

Caratteristiche infezioni da *Stenotrophomonas maltophilia*

- Opportunistiche e nosocomiali
- Polmoniti e sepsi
- Presentano resistenza intrinseca e acquisita agli antibiotici, compresi i carbapenemi
- Problemi: mancano indicazioni standardizzate per distinguere tra colonizzazione e infezione, e per guidare la terapia antibiotica

Fattori di rischio per infezioni da *S.maltophilia*



medicina

MDPI

Systematic Review

Hemorrhagic Pneumonia Caused by *Stenotrophomonas maltophilia* in Patients with Hematologic Malignancies—A Systematic Review and Meta-Analysis

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Abstract: *Background and Objectives:* There is a need for information regarding the clinical picture of hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in patients with hematologic malignancies. In this study, we aimed to investigate the risk factors associated with hemorrhagic pneumonia caused by *Stenotrophomonas maltophilia*. *Materials and Methods*: A review of the clinical picture of hemorrhagic pneumonia based on reported cases in the literature was performed. In addition, patients with hematologic malignancies who had a *Stenotrophomonas maltophilia* infection were included in the meta-analysis to evaluate risk factors for hemorrhagic pneumonia. *Results*: A total of 91 patients had hemorrhagic pneumonia. Acute myeloid leukemia was present in 57 patients (62.6%). Those with bacteremia accounted for 94%, while those with neutropenia accounted for 95% and those with thrombocytopenia accounted for 86.7%. Hemorrhagic pneumonia was a risk factor for mortality of *Stenotrophomonas maltophilia* infection in patients with hematologic malignancies. Neutropenia and thrombocytopenia were identified as risk factors for hemorrhagic pneumonia. *Conclusions*: *Stenotrophomonas maltophilia* bacteremia with hemorrhagic pneumonia in patients with hematologic malignancies is a situation with rapid development and high mortality. Neutropenia and thrombocytopenia were risk factors for hemorrhagic pneumonia in patients with hematologic malignancies and with *Stenotrophomonas maltophilia* bacteremia; thus, these patients should be managed with caution.

Keywords: *Stenotrophomonas maltophilia*; hematologic malignancy; hemorrhagic pneumonia; neutropenia; thrombocytopenia

Mortalità: 86%

check for updates

Citation: Huang, C.; Kuo, S.; Lin, L. Hemorrhagic Pneumonia Caused by *Stenotrophomonas maltophilia* in Patients with Hematologic Malignancies—A Systematic Review and Meta-Analysis. *Medicina* **2024**, *60*, 162. https://doi.org/10.3390/medicina60010162

Mortalità associata a infezioni da *S.maltophilia*

- Mortalità complessiva: per tutte le cause 18-69% (attribuibile 24-58%)
- Polmonite: mortalità per tutte le cause 23-86% (più alta in sepsi concomitante e nei pazienti oncologici)
- Sepsi: mortalità per tutte le cause 14-69%

Brooke, Clin Microbiol Rev 2021

Terapia *S.maltophilia*: più domande che risposte

- Nessun Trial Clinico Randomizzato (RCT) fornisce dati a supporto di un trattamento specifico

- Negli RCT più recenti, *S.maltophilia* è una causa non comune di infezione →
- studio CREDIBLE: solo 5 pazienti
- studio APEKS-NP: solo 1 paziente

- Data la relativa bassa frequenza di infezione, un RCT è difficile sia da disegnare che da completare

Breakpoints microbiologici *Stenotrophomonas*

Table 2
Comparison between EUCAST and CLSI breakpoints

Antibiotic		Interpretative categories and MIC breakpoints (mg/L)				
		EUCAST		CLSI		
		S	R	S	I	R
Cefiderocol[a]	(≤0,5)	—	—	≤1	—	—
Ceftazidime[b]		—	—	— (≤4)	—	—
Levofloxacin[c]	(<0,5)	—	—	≤2	4	≥8
Minocycline		—	—	≤1	2	≥4
Ticarcillin-clavulanate		—	—	≤16/2	32/2–64/2	≥128/2
Trimethoprim-sulfamethoxazole[d]		≤0.001/0.019	>2/38	≤2/38	—	≥4/76

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

[a] EUCAST includes the following text: 'There is insufficient clinical data to determine a clinical breakpoint. Isolates with MIC values ≤ 0.5 mg/L are mostly devoid of resistance mechanisms. Isolates with MICs 1–2 mg/L have acquired resistance mechanisms which may result in impaired clinical response. Isolates with MIC values > 2 mg/L will likely be resistant.'

[b] Ceftazidime breakpoints were removed from CLSI in 2024. Prior breakpoints were susceptible ≤4 mg/L, intermediate 8 mg/L, and resistant ≥8 mg/L.

[c] CLSI includes the following text: 'Levofloxacin should not be used alone for antimicrobial therapy.'

[d] CLSI includes the following text: 'Trimethoprim–sulfamethoxazole should not be used alone for antimicrobial therapy.'

Trimethoprim-sulfametossazolo (TRS)

- Primo farmaco storicamente consigliato dal 1973, nonostante non ci siano mai stati RCT che dimostrino la superiorità di TRS sugli altri antibiotici

- Resistenza globale tra 2000 e 2020 su oltre 10.000 isolati: 9.2%
- Dose consigliata: 15 mg/kg/d trimethoprim (BATTERIOSTATICO)

- La resistenza può svilupparsi anche in corso di trattamento:

- in uno studio retrospettivo osservazionale: l'8% dei pazienti con polmonite da *S. maltophilia* trattati con TRS senza eradicazione microbiologica, ha sviluppato resistenza a tale farmaco

Brooke, CMR 2021; Maraolo, Antibiotics 2023

Levofloxacina (LVX)

- Sensibilità a livello globale con il cut-off proposto dal CLSI: 78-88%

- La resistenza può svilupparsi anche in corso di trattamento:

-in uno studio retrospettivo osservazionale, >50% pazienti trattati con LVX come terapia di prima linea, che ha poi sviluppato una batteriemia, ha dimostrato resistenza a LVX

- in un altro studio retrospettivo osservazionale, il 20% dei pazienti con polmonite da *S. maltophilia,* trattati con LVX senza eradicazione microbiologica, ha sviluppato resistenza ai fluorochinoloni

Cho, AAC 2014; Nys, AAC 2019

Table 3

Recent analyses of therapeutic agents for *Stenotrophomonas* infections

First author Year [Reference]	Comparison	Type of analysis	Infection types	Outcome measured and findings	Conclusion
Ko 2019 [16]	Fluoroquinolones (mainly ciprofloxacin (CIP) and levofloxacin (LEV) vs Trimethoprim-sulfamethoxazole (TRS)	Meta-analysis 14 studies included	All	30-day mortality (n/N) CIP 19/114 (17%) LEV 52/187 (28%) TRS 111/332 (33.4) Odds ratio: FQs vs TRS 0.68 (0.53-0.97)	Fluoroquinolones superior to trimethoprim-sulfamethoxazole in terms of 30-day mortality
Maraolo 2023 [18]	Fluoroquinolones (FQ) vs Trimethoprim-sulfamethoxazole	Meta-analysis 24 studies included	All	Monotherapy 7 to 30-day mortality (n/N) FQ 143/1103 (13%) TRS 247/1304 (19%) Odds ratio: FQs vs TRS 0.62 (0.39-0.99)	Fluoroquinolones superior to trimethoprim-sulfamethoxazole in terms of 7 to 30-day all-cause mortality
Almangour 2024 [21]	Trimethoprim-sulfamethoxazole versus levofloxacin	4-centre retrospective	All	Clinical success (n/N) TRS 173/316 (55%) LEV 35/55 (64%) Odds ratio 0.70 (0.37-1.31) 30-day mortality TRS 88/316 (28%) LEV 14/55 (25%) Odds ratio 1.13 (0.59-2.18)	No difference between levofloxacin and trimethoprim-sulfamethoxazole in terms of clinical failure or 30-day mortality rates

REVIEW

Effective strategies for managing trimethoprim-sulfamethoxazole and levofloxacin-resistant *Stenotrophomonas maltophilia* infections: bridging the gap between scientific evidence and clinical practice

David Mokrani[a] *and Charles-Edouard Luyt*[a,b]

Purpose of review
To discuss the therapeutic options available for the management of difficult-to-treat strains of *Stenotrophomonas maltophilia* (*Sma*), namely those resistant to trimethoprim-sulfamethoxazole and fluoroquinolones.

Recent findings
Recent pharmacological studies have highlighted the fact that current breakpoints for first-line antibiotics against *Sma* are too high. In light of these data, it is likely that the prevalence of difficult-to-treat (DTR) *Sma* is underestimated worldwide. Two promising alternatives for treating DTR strains are cefiderocol and the combination of aztreonam and an L2 inhibitor. However, clinical trials are currently very limited for these antibiotics and no comparative studies have been carried out to date. It is important to note that the clinical efficacy of cefiderocol appears to be inferior to that initially anticipated from in-vitro and animal studies. Consequently, minocycline and ceftazidime may remain viable options if they are used against strains with a low minimum inhibitory concentration. We advise against the use of intravenous polymyxins and tigecycline. Finally, recent literature does not support the systematic use of combination therapy or long-course treatments. In the coming years, phage therapy may become a promising approach against DTR *Sma* infections.

Summary
Overall, clinical comparative studies focused on DTR strains are required in order to provide more accurate and actionable information for therapeutic decisions.

Keywords
aztreonam, cefiderocol, ceftazidime-avibactam, difficult-to-treat, multidrug resistance, *Stenotrophomonas maltophilia*

Cefiderocol demonstrated *in vitro* activity against ***S. maltophilia*** isolates that were non-susceptible to levofloxacin and/or trimethoprim/sulfamethoxazole

N=37

Isolates	Cefiderocol[a]	Trimethoprim/ sulfamethoxazole	Levofloxacin	Minocycline	Ceftazidime	Polymyxin B
	% susceptible					
Levofloxacin- and/or trimethoprim/ sulfamethoxazole-resistant *S. maltophilia*	100	37.8	35.1	97.3	16.2	0

Based on CLSI susceptibility breakpoints[a]

In vitro activity shown as green (>80%), amber (30–80%), or red (<30%)

[a]Cefiderocol MIC: ≤4 mg/L; ceftazidime MIC: ≤8 mg/L; levofloxacin MIC: ≤2 mg/L; minocycline MIC: ≤4 mg/L; trimethoprim/sulfamethoxazole MIC: ≤2/38 mg/L. A polymyxin B MIC of ≤2 mg/L was considered intermediate given the lack of a susceptible category in CLSI document

CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration

Biagi M, et al. *Antimicrob Agents Chemother.* 2020;64:e00559–20

Cefiderocol

- Ottima attività in vitro
- I dati sugli animali (topi neutropenici con polmonite) supportano l'uso di cefiderocol nell'uomo, anche se nell'uomo i dati non sono ancora conclusivi
- Possibile sinergia con altri farmaci anti-*Stenotrophomonas* come levofloxacina

- Non esistono kit commerciali affidabili per stabilire la sensibilità a cefiderocol: al momento necessaria microdiluizione in brodo
- L'EUCAST nella seconda metà del 2025 proporrà valori di breakpoint con cutoff epidemiologici con metodiche di diffusione su disco

Studi retrospettivi «real life» cefiderocol: *Perseus* & *Prove*

- Studio Perseus: Torre-Cisneros, Eur J Clin Microbiol Infect Dis 2025:

- 20 pazienti --> 55% polmonite, 25% sepsi
- Cura clinica 70%, mortalità a 28 gg 30%

- Studio Prove, *in corso*: dati preliminari Clancy, Infect Drug Res 2024

- 20 pazienti --> 40% polmonite, 30% sepsi
- Cura clinica 65%, mortalità a 28 gg 35%

Conclusions and guidance

There is only weak evidence to support treatment alternatives in *S. maltophilia* infections. Historically trimethoprim-sulfamethoxazole has been regarded the drug of choice, but retrospective clinical data question whether this agent is preferable to other agents.

Alternatives which have been tried and discussed are fluoroquinolones (mainly levofloxacin and moxifloxacin), intravenous minocycline and cefiderocol, but there is scant or no clinical evidence for the usefulness of either of these or for a correlation between susceptibility test results and clinical outcome. Tigecycline may also be an option where intravenous minocycline is unavailable. The role of fluoroquinolones is challenging to assess due to unfavourable PK/PD despite meta-analyses and other studies suggesting superiority to trimethoprim-sulfamethoxazole.

Currently, cefiderocol is the agent with the most favourable *in vitro* activity and may be preferable to the traditional trimethoprim-sulfamethoxazole as first line therapy. However, uncertainty will persist until there are clinical studies to support this conclusion [40]. In summary, the efficacy of all agents and combinations is uncertain and treating physicians should be vigilant in case therapeutic responses are unconvincing.

References

1. Abbott IJ, Slavin MA, Turnidge JD, Thursky KA, Worth LJ. *Stenotrophomonas maltophilia*: emerging disease patterns and challenges for treatment. Expert Rev Anti Infect Ther. 2011; 9:471-88
2. Brooke JS. *Stenotrophomonas maltophilia*: Advances in the microbiology of *Stenotrophomonas maltophilia*. Clin Microbiol Rev 2021; 34:e00030-19
3. Maraolo AE, Licciadi F, Gentile I, Saracino Am Belati A, Bavaro DF. *Stenotrophomonas maltophilia* Infections: A Systematic Review and Meta-Analysis of Comparative Efficacy of Available Treatments, with Critical Assessment of Novel Therapeutic Options. Antibiotics 2023; 12:910.
4. Wei C, Ni W, Zhao J, Cui J. Evaluation of trimethoprim-sulfamethoxazole (SXT), minocycline, tigecycline, loxifloxacin and ceftazidime alone and in combinations for SXT-susceptible and SXT-resistant *Stenotrophomonas maltophilia* in in vitro time-kill experiments. PLoS ONE 2016, 11, e0152132.
5. Lasko MJ, Gethers ML, Tabor-Rennie JL, Nicolau DP. In vitro time-kill studies of trimethoprim/sulfamethoxazole against *Stenotrophomonas maltophilia* using cation-adjusted Mueller-Hinto broth and IsoSensitest broth. Antimicrob Agents Chemother 2022; 66:e2167-21

Aztreonam/avibactam

- Aztreonam dato in combinazione con avibactam contrasta con efficacia le betalattamasi L1 e L2 codificate nei cromosomi di *Stenotrophomonas*:

- aztreonam non viene inattivato da bla L1 (MBL)
- avibactam inibisce la bla L2 (che inattiverebbe aztreonam)

- Avibactam privilegiato rispetto a clavulanato per la > affinità alla bla L2 e la > penetrazione nell'ELF degli alveoli polmonari

- Non ci sono dati definitivi a supporto di un determinato breakpoint: efficacia riportata è > 99% dei casi in vitro con MIC ≤8 mg/l

Mojica JAC AR 2022; Ruddy, IdCases 2024; Sader IJID 2025

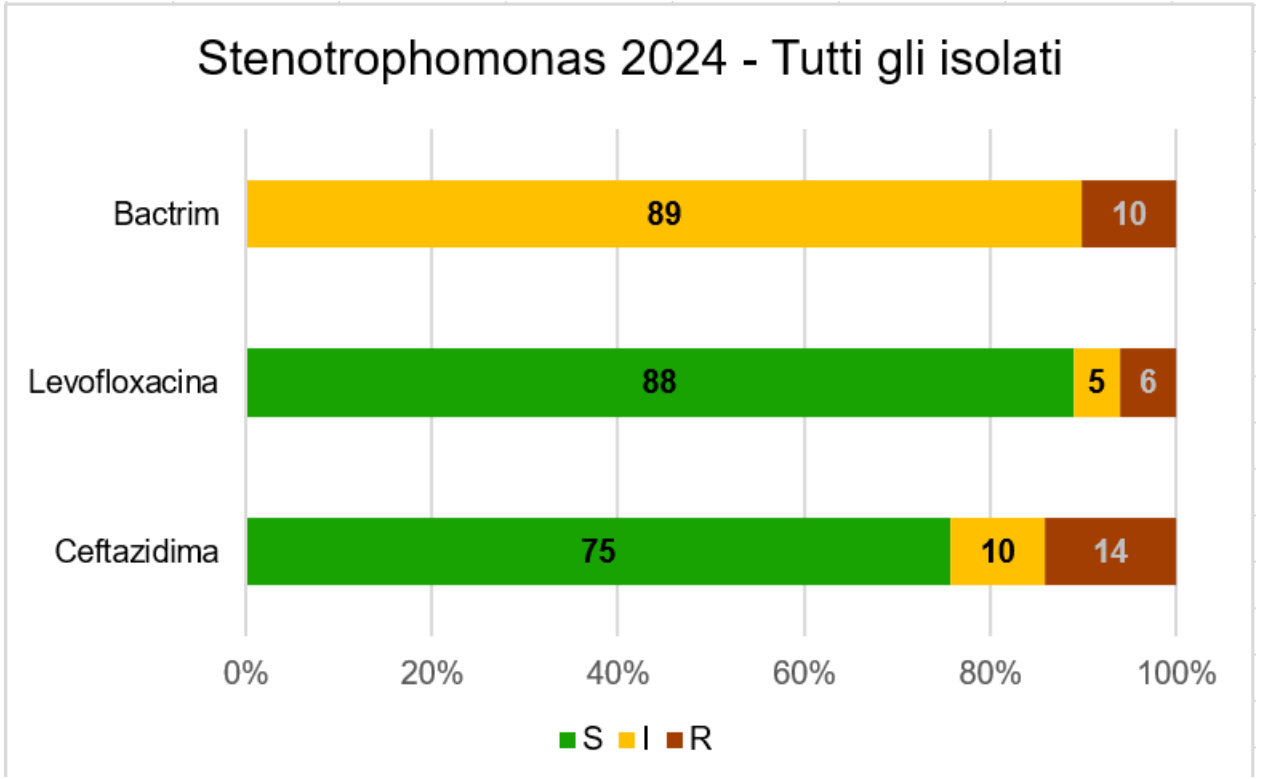
Minociclina

- Dose non-standard: 200 mg os/ev ogni 12 ore
- Il CLSI nel 2024 ha ridotto il breakpoint della minociclina per *S. maltophilia* da 4 mg/L a 1 mg/L
- Sensibilità è passata col nuovo breakpoint da 77 a 35% in Asia (India), mentre rimasta stabile negli USA: 93.8%
- Ceppi resistenti a minociclina possono essere sensibili a eravaciclina

Crowley, Eur J Clin Microbiol Infect Dis 2025; Al Musawa, Infect Dis Ther 2025

Asl Città di Torino e *Stenotrophomonas maltophilia*

Isolati Sma 2024:	**99**
tratto respiratorio	59
sangue	2
urine	6
altri materiali	14
tampone faringeo	6
tampone rettale	12



Courtesy Alessia Di Vincenzo, MD

Algoritmo proposto per *S. maltophilia*

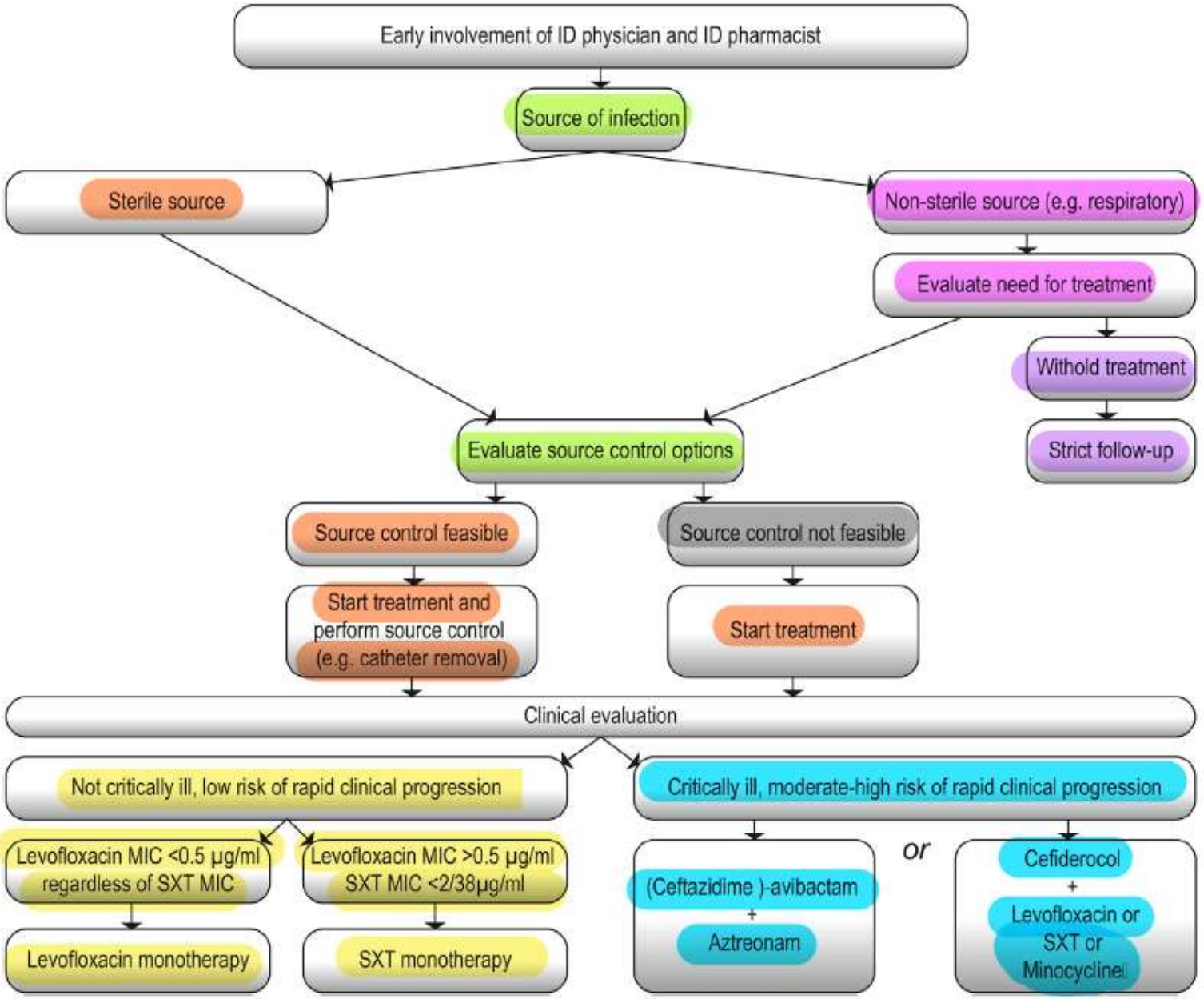


Fig. 2. Approach to the treatment of *Stenotrophomonas maltophilia* infections. SXT, trimethoprim–sulfamethoxazole.

Monardo & Van Duin, CMI 2025, *in press*

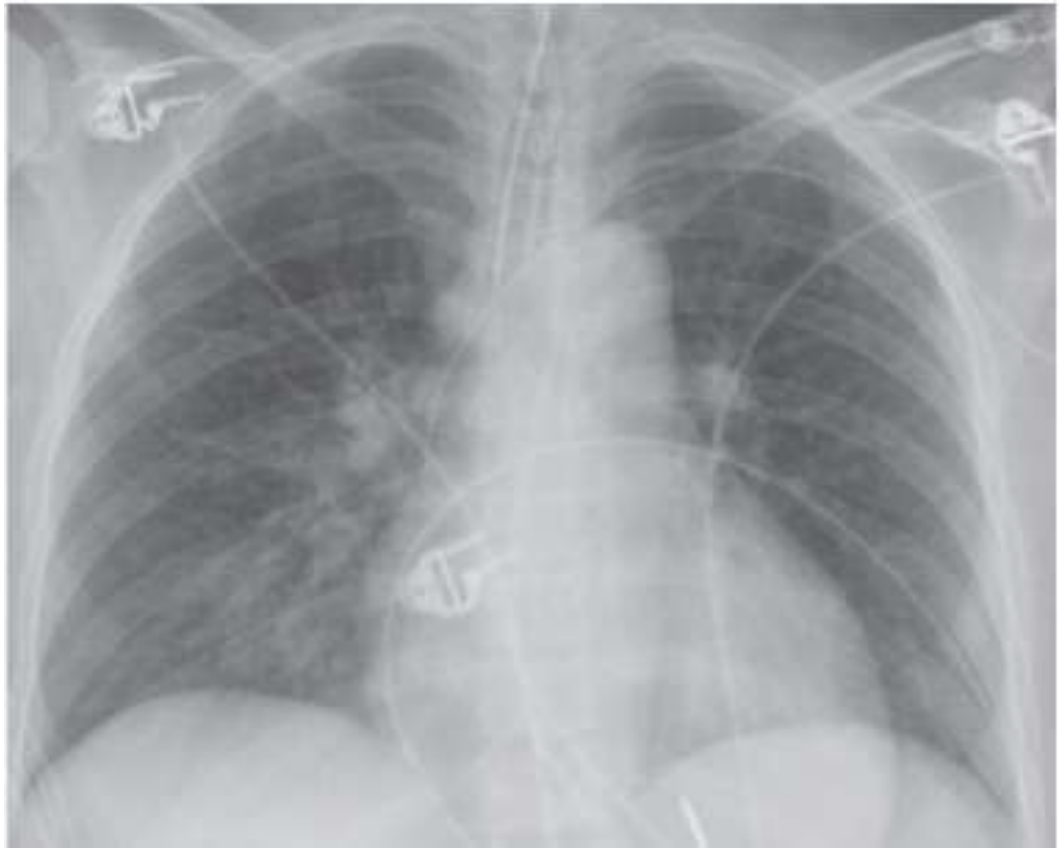
Caso clinico: esito

- Dopo 48 ore: emocolture positive per *Stenotrophomonas maltophilia*
- In attesa dell'antibiogramma: a piptazo si associa cotrimossazolo

- Dopo 24 ore: il paziente non migliora, e l'ABG evidenzia sensibilità a cefiderocol e levofloxacina
- STOP piptazo e TRS

- INIZIA cefiderocol 2 g in 3 h ogni 8 ore + levofloxacina 750 mg/ 24 ore

- Emocolture si negativizzano a 48 ore
- PCR si normalizza con sfebbramento stabile in pochi giorni
- Rx in avanzato miglioramento



<u>DURATA terapia : 10 giorni</u>

Estubato
Dimesso

Conclusioni

- *Stenotrophomonas maltophilia* è una causa infrequente di infezione

- Ci sono pochi dati disponibili per stabilire il trattamento migliore:

- nei pazienti non critici: sono opzioni di prima linea

*levofloxacina e trimethoprim-sulfametossazolo

- nella malattia grave: consigliabile terapia con i farmaci più attivi

* cefiderocol (+ levofloxacina o TMS o minociclina)
* aztreonam/avibactam (o aztreonam + ceftazidime-avibactam)

Grazie per l’attenzione!